Peripheral Sensory Nerve Dysfunction in Children and Adolescents with Type 1 Diabetes Mellitus

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The aim of the present study was to investigate peripheral sensory nerve function in diabetic children and adolescents without neurological symptoms. Ninety-two children and adolescents with Type 1 (insulin-dependent) diabetes mellitus (mean ± SD age: 14.2 ± 2.1 years, diabetes duration: 5.8 ± 3.0 years) and 80 healthy control subjects (age: 13.8 ± 2.2 years) matched for age, sex, body mass index, and height standard deviation score were involved in the study. Using a sine-wave transcutaneous stimulator, current perception threshold (CPT) testing at 2000, 250 and 5 Hz was performed on the left median and peroneal nerves. Diabetic children had increased CPT at 2000 Hz on both nerves as compared to the control group (median (interquartile range), median nerve: 2.43 (2.20–3.43) vs 1.80 (1.51–2.60) mA, $p = 0.02$; peroneal nerve: 3.51 (2.81–4.82) vs 2.70 (2.04–3.70) mA, $p = 0.01$). Twenty-one (23 %) of patients had CPT values higher than that of any healthy individual. Of these, elevated CPT was observed in 9 (9.8 %) patients on the median nerve, in 8 (8.7 %) patients on the peroneal nerve, and in 4 (4.3 %) patients on both median and peroneal nerves. Using multiple logistic regression analysis, worse long-term metabolic control and advanced puberty were independently predictive of peripheral sensory nerve dysfunction as the dependent variable (adjusted OR (95 % CI): 3.4 (1.2–6.2), $p = 0.01$, and 2.8 (1.1–5.6), $p = 0.03$, respectively). In conclusion, evidence of peripheral sensory nerve dysfunction is not rare in children and adolescents with diabetes and can be demonstrated by CPT testing in asymptomatic patients. Poor metabolic control is a risk factor for such subclinical neuropathy, and pubertal development may be involved in the pathogenesis of diabetic peripheral neuropathy. © **1998 John Wiley & Sons, Ltd.**

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Introduction

In adults, peripheral neuropathy has been shown to be a common complication of Type 1 (insulin-dependent) diabetes mellitus.[1,2] Little information is available in children with diabetes. Overt neurological disturbances are uncommon in diabetic children and adolescents,[3] however, subclinical signs of peripheral nerve damage appear to be present in this age group.[4–7] Most of the earlier studies used nerve conduction velocity assessments which, although reasonably reproducible, quantifies only the function of large myelinated fibres. Few studies have applied quantitative sensory nerve testing in children and adolescents with diabetes. These tests have the advantage of being non-invasive, measure small nerve function and have proved to be a sensitive method for early detection of subclinical sensory neuropathy in diabetic children.[8,9] As diabetic neuropathy involves the entire range of nerve fibres of varying diameter[10,11] there is need for a method to obtain quantitative measures of nerve integrity from different nerve fibre types. The neurometer is a device for non-invasive assessment of diabetic neuropathy which measures the sensitivity to electric current or current perception threshold (CPT).[12] It has the advantage of neuroselectivity and can test different types of nerve fibres by using different frequencies of electric stimulus: high frequencies for large fibres and low frequencies for small unmyelinated nerve fibres.[13,14] As no previous data on CPT testing in children are available, in the present study we set out to assess peripheral sensory nerve function in diabetic children and adolescents without clinical symptoms of neuropathy and to investigate the relations between CPT and various clinical characteristics of the patients.

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Patients and Methods

Study populations

Ninety-two children and adolescents with Type 1 diabetes mellitus (aged 6 to 18 years; duration of diabetes ranging from 1 to 17 years) and 80 healthy subjects (aged 6 to 18 years) were studied. The patients were recruited from the people regularly attending the diabetes outpatient clinic at our hospital and the non-diabetic controls from local schools. Since, in Hungary, all children and adolescents with diabetes within a geographic region attend the same hospital clinic, this material is unselected. The diabetic and healthy groups were matched for age by 2-year intervals and within age bands for sex, body mass index (BMI) by 2 kg m^{-2} and height standard deviation score (SDS) by 0.1 intervals (Table 1). The BMI represents the ratio between weight (kg) and height squared (m^2). Height SDS was calculated according to the formula: $(X_i\text{-}M_x)/S_x$, where X_i is the actual height, M_x is the mean height for that age and sex, and S_x is the standard deviation corresponding to that age and sex.

All patients were treated with combinations of short and intermediate acting human insulin injected two or four times daily. None had any disorder apart from diabetes, and none had clinical symptoms or signs of neuropathy or angiopathy. Patients with microalbuminuria (defined as 24-h albumin excretion >20 μg min^{-1} on two consecutive occasions 2–4 weeks apart), subclinical retinopathy (on fluorescein angiography) or cardiovascular autonomic dysfunction (assessed by cardiovascular tests) were excluded from the study.[15] Neither the healthy nor the diabetic subjects had been treated with any drugs (except for insulin) during the study or during the preceding 2 weeks. All patients were in stable metabolic condition with no ketonuria or hypoglycaemia at the time of the investigation. Diabetic children had capillary blood glucose between 5 and 12 mmol l^{-1} prior to nerve function testing. Studies were not carried out on patients who presented with blood glucose outside this range and a new appointment was made within 2 weeks. The diabetic group had mean ± SD blood glucose of 8.4 ± 1.6 mmol l^{-1} at the time of study.

Patients had formal physical examination before CPT testing. Pubertal development was assessed according to Tanner criteria (breast and pubic hair stages for girls; genitalia and pubic hair stages for boys).[16] Blood pressure was measured using a sphygmomanometer with the subject seated. Long-term metabolic control was estimated by mean glycated haemoglobin level over 1 year measured 3 monthly. All subjects and their parents gave informed consent, and the study was approved by the regional ethics committee.

Table 1. Characteristics of groups studied (mean ± SD)

	Diabetes ($n = 92$)	Control ($n = 80$)
Gender (M/F)	46/46	40/40
Age (yr)	14.2 ± 2.1	13.8 ± 2.2
BMI (kg m^{-2})	19.1 ± 2.3	19.4 ± 2.5
Height SDS	0.15 ± 0.3	0.14 ± 0.4
Diabetes duration (yr)	5.8 ± 3.0	–

BMI, body mass index; SDS, standard deviation score.

Quantitative Sensory Nerve Testing

Assessment for peripheral sensory nerve function was performed by the Neurometer CPT (Neurotron Inc., Baltimore, USA)[12,17] in a quiet room, with the subject seated. The equipment is a neuroselective transcutaneous electric stimulator which generates a sinusoidal waveform from a constant current stimulator, adjustable from 0 to 10 milliamperes (mA). The lowest level of painless electric stimulus required to evoke a sensation (current perception threshold, CPT) was determined for 5 Hz, 250 Hz, and 2000 Hz frequencies at two test sites: the left index finger and the left great toe (median and peroneal nerves, respectively). Two small gold plated surface electrodes were applied: one on the lateral and the other on the medial aspect of the finger or toe. The electrodes were connected to the Neurometer device and the intensity of the electric stimulus was initially increased until a specific sensation was reported by the subject. Short stimuli were then applied at progressively lower amplitudes until a minimal, but consistent, threshold was detected. The device has a 'dummy' switch to allow the on/off status of the machine to be concealed from the subject, and a forced choice method was used to confirm the minimum threshold for perception.

Ranges of CPT results obtained in the healthy control group aged 6 to 18 years were considered normal. Age, sex, BMI, and height SDS had no effect on CPT results in healthy children and adolescents; reference data are given in Table 2. CPT values of diabetic subjects falling above the normal range were considered abnormally elevated threshold and defined as hypoaesthesia. Reproducibility of the CPT measures was examined by reassessing five healthy subjects. Each subject was reassessed twice after the initial investigation at 2-week

Table 2. Reference values for current perception threshold (CPT) results obtained in healthy children and adolescents aged 6 to 18 years

	CPT (mA) median	Range
Median nerve		
5 Hz	0.78	0.42–1.70
250 Hz	0.80	0.46–1.73
2000 Hz	1.80	1.22–3.40
Peroneal nerve		
5 Hz	0.97	0.38–2.12
250 Hz	1.36	0.40–2.62
2000 Hz	2.70	1.38–4.70

intervals. The mean and standard deviation of the three measurements for each person was calculated and the coefficient of variation expressed as a percentage (SD/mean × 100). The coefficients of variation for the CPT measures were as follows: 8 % at 2000 Hz, 12 % at 250 Hz, and 18 % at 5 Hz.

Laboratory Measurements

Capillary blood glucose concentrations were determined by means of a glucose reflectance meter (One Touch, Lifescan, Johnson and Johnson, Milpitas, USA). Glycated haemoglobin (HbA_1) was measured by an ion capture assay (IMx Glycated Haemoglobin Assay, Abbott Laboratories, Chicago, USA), with a non-diabetic range of 4.8 to 7.8 %.

Statistical Analysis

Clinical and biochemical characteristics of study groups are given as mean ± SD and CPT results are expressed as median and interquartile range. Distribution was tested for each variable by the Kolmogorov-Smirnov test. Differences between groups were tested by χ^2 test and the Student's *t*-test or Mann-Whitney rank sum test for normal or non-normal data, respectively. Statistical associations were established by linear regression analysis for continuous data. Multiple logistic regression analysis was applied for discrete binary variables and odds ratios (OR) with 95 % confidence intervals (CI) were calculated. A *p* value less than 5 % was considered statistically significant.

Results

On the median nerve, diabetic children had significantly increased CPT values at 2000 Hz frequency as compared to the healthy control group (2.43 (2.20–3.43) vs 1.80 (1.51–2.60) mA, $p = 0.02$). CPT values at 250 Hz and 5 Hz frequencies were slightly higher in the diabetic group than in the control group, but the differences were not statistically significant (1.10 (0.95–1.72) vs 0.80 (0.63–1.27) mA, $p = 0.08$ and 0.98 (0.82–1.51) vs 0.78 (0.60–1.24) mA, $p = 0.11$, respectively)(Figure 1).

On the peroneal nerve, CPT at 2000 Hz of diabetic children was significantly higher compared to CPT of healthy children (3.51 (2.81–4.82) vs 2.70 (2.04–3.70) mA, $p = 0.01$). Although CPT at 250 Hz and 5 Hz frequencies were higher in the diabetic group than in the control group, these differences did not reach statistical significance (1.60 (1.02–2.45) vs 1.36 (0.88–1.99) mA, $p = 0.07$ and 1.19 (0.80 - 2.01) vs 0.97 (0.68 - 1.55) mA, $p = 0.10$, respectively) (Figure 1).

Using reference ranges obtained in the healthy subjects, 21 diabetic patients (23 %) had hypoaesthesia defined as one or more abnormally elevated CPT result(s). Of these, elevated CPT values were observed in 9 (9.8 %) patients on the median nerve, in 8 (8.7 %) patients on the peroneal nerve, and in 4 (4.3 %) patients on both median and peroneal nerves. The frequency of elevated CPT results at the three different frequencies studied were as follows: median at 2000 Hz, $n = 8$ (8.7 %), at 250 Hz, $n = 8$ (8.7 %), at 5 Hz, $n = 4$ (4.3 %); peroneal at 2000 Hz, $n = 7$ (7.6 %), at 250 Hz, $n = 5$ (5.4 %), at 5 Hz, $n = 2$ (2.2 %). Altogether, median nerves were affected slightly more frequently than peroneal nerves, but the difference was not significant (22 % vs 15 %, $p = 0.1$).

Characteristics of patients assigned into two groups according to the presence or absence of abnormally elevated CPT can be seen in Table 3. Patients with elevated CPT results had significantly higher mean glycated haemoglobin level over 1 year than those with normal sensory nerve function (13.0 ± 1.9 % vs 8.6 ± 2.4 %, $p = 0.03$). Nevertheless, late pubertal patients (Tanner stage 4–5) had higher CPT values on the peroneal nerve at 2000 Hz after controlling for glycated haemoglobin than prepubertal or early pubertal (Tanner stage 1–3) patients (3.61 (2.92–5.01) vs 2.66 (2.12–4.14) mA, $p = 0.01$). Using multiple logistic regression analysis, mean glycated haemoglobin over 1 year (>12 % vs <8 %) and late pubertal stages (T_{4-5} vs T_{1-2}) proved to be independently predictive of the presence of at least one elevated CPT result when the latter was entered as the dependent variable (adjusted OR (95 % CI): 3.4 (1.2–6.2), $p = 0.01$, and 2.8 (1.1–5.6), $p = 0.03$, respectively). Gender, BMI, height SDS, diabetes duration, insulin dosage, blood glucose level at the time of testing, and systolic and diastolic blood pressure were not associated with sensory nerve dysfunction in this multivariate analysis.

Discussion

In this study we demonstrated increased CPT at 2000 Hz on both peroneal and median nerves in diabetic children and adolescents, an early sign of peripheral large myelinated sensory nerve dysfunction. Moreover, hypoaesthesia defined as one or more abnormally elevated CPT finding was found in 23 % of the diabetic cohort. Peripheral sensory nerve dysfunction was associated with poorer long-term metabolic control and advanced puberty.

Our present finding of 23 % of diabetic children having evidence of early sensory nerve dysfunction is consistent with previous reports on quantitative sensory tests in childhood diabetes.[8,9] In studies where both upper and lower limbs were investigated, the lower limb showed poorer overall results and more abnormalities.[7,9,14] Similarly, in the present study both the diabetic and healthy subjects exhibited higher peroneal than median CPT results at all the three frequencies studied, although abnormal findings were not more frequently seen on the peroneal nerves. In keeping with other studies[5,6,7], we observed a clear relationship between sensory nerve function and long-term metabolic control so that subjects with the worst CPT results had poorest

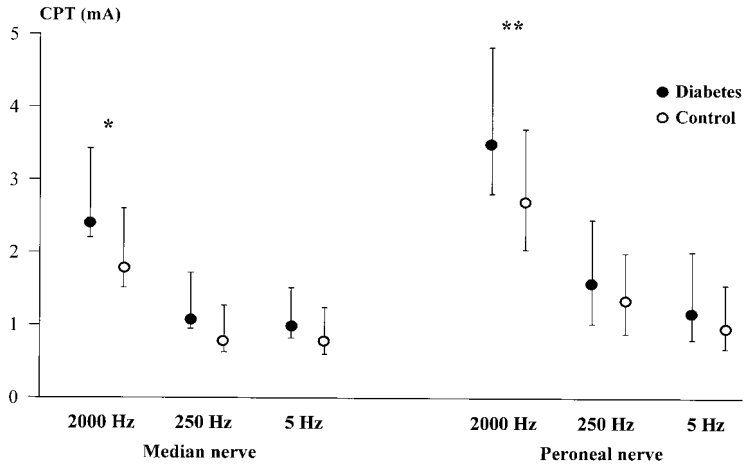

Figure 1. Current perception threshold (CPT) in diabetic and control groups (median and interquartile range); $^{*}p = 0.02$; $^{**}p = 0.01$

Table 3. Characteristics of diabetic patients with and without abnormal current perception threshold (CPT) result (mean ± SD)

	With abnormal CPT ($n = 21$)	Without abnormal CPT ($n = 71$)
Age	14.9 ± 2.1	13.9 ± 2.3
Gender (M/F)	13/8	37/34
BMI (kg m^{-2})	19.3 ± 2.4	19.0 ± 2.5
Height SDS	0.13 ± 0.3	0.15 ± 0.3
Diabetes duration (yr)	6.4 ± 2.8	5.6 ± 3.1
Mean HbA_1 over 1 year (%)	13.0 ± 1.9[a]	8.6 ± 2.4
Daily dose of insulin (U kg^{-1})	0.90 ± 0.5	0.88 ± 0.3
Blood glucose (mmol l^{-1})	10.3 ± 2.5	9.9 ± 2.6
Blood pressure (mmHg)		
systolic	117.1 ± 4.2	115.3 ± 5.1
diastolic	74.2 ± 4.8	72.9 ± 4.6

BMI, body mass index; SDS, standard deviation score. [a]$p = 0.03$

control. In a recent study, we found a similar association between autonomic dysfunction and long-term metabolic control[15] and these support the view that the development of neurological complications depend on the long-term metabolic control of diabetes.[18] On the other hand, in multivariate analysis no relationship was found between blood glucose concentration at the time of testing and nerve function measures, which suggests that ambient blood glucose level does not have major effect on CPT results.

There is evidence to suggest that the pubertal process is a significant risk factor for the development and progression of diabetic microvascular complications.[19–23] In the present study, the association between abnormal CPT results and late pubertal stages suggests that pubertal development may be involved in the pathogenesis of diabetic peripheral sensory neuropathy. Other groups have noted a relationship between puberty and peripheral nerve dysfunction.[5,8,9] Hoffman *et al*. found that the increase in prevalence of delayed nerve conduction velocities occurs during the middle teen years of diabetic children.[5] Sosenko *et al*. observed a strong correlation between the vibration perception threshold and glycaemia in the postpubertal but not in the younger patients.[8] In a very recent study by Olsen *et al*., advanced pubertal stages were also associated with poorer vibration perception threshold findings in diabetic children.[9] Interestingly, diabetic autonomic nervous system dysfunction did not seem to be related to puberty.[15,24] These data suggest that puberty may initiate or accelerate the neuropathic process, although peripheral and autonomic nerves may not be equally affected. The mechanism for this is not known. Sex steroids, growth hormone and IGF-I, whose levels are increased during the pubertal process, are possible contributors.[25–28] Hyperglycaemia itself may also play a role. Peripheral nerve function in humans matures to adult levels by late childhood and early adolescence[29] and animals with maturing peripheral nerves exposed to hyperglycaemia manifest greater pathological alterations than those that occur when adult nerves are exposed to similarly elevated glucose concentrations.[30] These studies raise the possibility that nerves are more susceptible to diabetes during the pubertal years. Further experimental and prospective clinical studies are necessary to assess the role of pubertal process in the pathogenesis of diabetic neuropathy.

The differential involvement of small and large fibre populations necessitates multi-modal evaluation for a full assessment of peripheral nerve integrity in diabetes. Current perception threshold testing is a relatively new,

non-invasive technique that has been reported to measure sensory nerve integrity reliably[12,13,31], although one study has found that its sensitivity is worse than the conventional (and time consuming) vibratory and thermal threshold measurements.[32] Low frequency (5 Hz) stimulus detects abnormalities that correlate with small unmyelinated fibre functioning, as determined with quantitiative thermal threshold measures and pain sensation. Higher frequency (250 Hz and 2000 Hz) stimulus detects abnormalities correlated with larger fibre functioning, as measured by quantitative vibratory and sensory nerve conduction evaluations.[31] Our finding of impaired CPT at 2000 Hz may have particular importance as large nerve dysfunction has a pivotal role in the pathogenesis of diabetic foot syndrome.[33] Small nerve dysfunction could also have been present in our patients, possibly missed because of the highest coefficient of variation of CPT at 5 Hz. CPT testing as used in the present study was easy to perform, no discomfort was reported and otherwise showed an acceptably low intra-patient variation in children and adolescents, consistent with results in adults.[14,31] Its further advantages are that it does not need a highly trained examiner and, as normal childhood data are not influenced by age, it should be useful for prospective studies.

In conclusion, peripheral sensory nerve dysfunction is not rare in diabetic children and adolescents and CPT testing is an easy and reliable method for its early detection in asymptomatic young patients. Poor long-term blood glucose control is the most important risk factor, and the pubertal process may contribute to the evolution of diabetic peripheral nerve damage. Efforts should be made to maintain the best possible metabolic control to prevent or delay this diabetes-related complication. Further prospective studies are required to investigate the role of puberty in the pathogenesis of diabetic neuropathy.

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